The effect of chronic angiotensin I converting enzyme inhibition on the pressure–natriuresis relation was studied in Wistar-Kyoto and spontaneously hypertensive rats. Enalapril maleate (25 mg·kg⁻¹·day⁻¹ in drinking water) was started at 4–5 weeks of age. At 7–9 weeks of age, the pressure–natriuresis relation was studied while the rats were under Inactin anesthesia 1 week after the right kidney and adrenal gland were removed. Neural and hormonal influences on the remaining kidney were fixed by surgical renal denervation, adrenalectomy, and infusion of a hormone cocktail (330 µl·kg⁻¹·min⁻¹) containing high levels of aldosterone, arginine vasopressin, hydrocortisone, and norepinephrine dissolved in 0.9% NaCl containing 1% albumin. Changes in renal function resulting from alterations in renal artery pressure were compared between enalapril-treated and control rats. Mean arterial pressure (±SEM) under anesthesia was 118±5, 94±4, 175±3, and 124±2 mm Hg for control Wistar-Kyoto (n=10), enalapril-treated Wistar-Kyoto (n=10), control spontaneously hypertensive (n=9), and enalapril-treated spontaneously hypertensive (n=9) rats, respectively. When renal artery pressure was set at values above approximately 125 mm Hg, control spontaneously hypertensive rats excreted less sodium and water than control Wistar-Kyoto rats. Enalapril treatment resulted in a significant and similar shift to the left of the pressure–natriuresis relation in both strains of rats so that a lower renal artery pressure was required to excrete a similar amount of sodium when compared with their respective untreated controls. Over the pressure range where differences in the pressure–natriuresis relation were significant, both renal blood flow and glomerular filtration rate were autoregulated and similar in all four groups. The similar effect of enalapril on the pressure–natriuresis curve in Wistar-Kyoto and spontaneously hypertensive rats suggests that the renal effects of angiotensin II are not the primary reason for the difference in the pressure–natriuresis relation in control Wistar-Kyoto and spontaneously hypertensive rats in this preparation. (Hypertension 1991;17:54–62)

It has been suggested that elevated mean arterial pressure in spontaneously hypertensive rats (SHR) may be the result of an intrinsic abnormality in kidney function. According to this hypothesis, a decrease in the ability of the kidneys to excrete sodium and water will require an increase in arterial pressure to maintain fluid and electrolyte homeostasis. This concept is supported by the observation that the chronic arterial pressure–urinary output relation is shifted along the pressure axis in adult SHR compared with that in Wistar-Kyoto (WKY) rats. Similarly, in anesthetized SHR and WKY rats of various ages, the acute pressure–natriuresis curve for SHR, even before 5 weeks of age, was shifted significantly along the pressure axis compared with that seen for age-matched WKY rats. In the pressure–natriuresis model used, kidneys were denervated and plasma levels of catecholamines, vasopressin, aldosterone, and hydrocortisone were controlled, thereby suggesting that an intrarenal abnormality independent of neural and hormonal influence was responsible for the different pressure–natriuresis curves between these two strains of rats.

Chronic treatment of prehypertensive SHR with a converting enzyme inhibitor prevents the development of hypertension. Similarly, when adult SHR are treated with a converting enzyme inhibitor the arterial pressure is reduced significantly. These observations suggest that the renin-angiotensin system may play an important role in the onset and maintenance of hypertension in SHR, although no
difference exists between SHR and WKY rats for plasma renin activity, plasma angiotensin converting enzyme activity, or plasma levels of angiotensin I (Ang I) and II (Ang II). However, the content of Ang I and Ang II within the kidneys of 4–5-week-old SHR has been shown to be significantly higher than that in WKY rats despite similar kidney renin and converting enzyme activities between the two. In addition, binding studies have shown that Ang II receptor density in brush border membranes of SHR kidneys at 4 weeks of age and glomeruli of SHR at 6 weeks of age is higher when compared with age-matched WKY rats. These intrarenal conditions could lead to a decrease in sodium excretion directly through tubular mechanisms and indirectly through hemodynamic effects of Ang II, thus necessitating an elevated arterial pressure to maintain normal urinary excretion of sodium.

The present study was designed to investigate the effect of chronic converting enzyme inhibition with enalapril on the acute pressure–natriuresis curve of SHR in the developmental stage of hypertension to test the hypothesis that prevention of the rise in arterial pressure in SHR was associated with a shift in the pressure–natriuresis curve toward that of the normotensive control. Treated and untreated WKY rats were also used to test the hypothesis that enalapril-induced changes in the pressure–natriuresis response in the SHR were specific to that strain. If the data supported the latter hypothesis, then the difference in the pressure–natriuresis curves between untreated SHR and WKY rats could be attributed at least in part to the renin-angiotensin system.

Methods

Chronic Converting Enzyme Inhibition

Male SHR and WKY rats were ordered alternately in groups of six rats from Harlan Laboratories, Indianapolis, Ind., to arrive at 4–5 weeks of age. They were housed individually in suspended wire mesh cages and further divided randomly into two groups. One group received enalapril maleate (Merck Frosst Canada Inc., Point Claire, Quebec) to achieve a dose of about 25 mg·kg⁻¹·day⁻¹; the other group served as the drinking water with the untreated control group for each strain. Food was available ad libitum and water intake was monitored twice weekly. At this time, the rats were weighed and the average weekly tail-cuff pressure was calculated to represent the pressure for that week. Average weekly tail-cuff pressure was calculated using the two measurements made on separate days.

Experimental Preparation

The experimental preparation and protocol was essentially that described originally by Roman and Cowley and used previously in SHR and WKY rats. At 6–7 weeks of age, three rats were randomly selected for excision of the right adrenal gland and kidney through a lateral flank incision while they were under equithesin anesthesia (0.3 ml/100 g body wt i.p.) and then were allowed 7–10 days to recover. The right kidney and adrenal gland of the remaining three rats were removed 1 week later to be ready for experimentation in the second week of study. Therefore, the first three rats studied were 7–8 weeks old and the remaining three rats were 8–9 weeks old.

On the day of the experiment, the rats were anesthetized with Inactin (100 mg/kg body wt i.p., Byk-Gulden, Constance, FRG) and placed on a heated board; a tracheostomy was performed (PE-240 tubing) to facilitate breathing. The left jugular vein was cannulated with PE-60 tubing and a priming dose of 10% inulin in 0.9% saline (0.9% NaCl) was given. Catheters (PE-50) in the left carotid and femoral arteries were used to sample arterial blood and were also connected to pressure transducers (Statham P23DC, Statham Division, Gould Inc., Oxnard, Calif.) for recording arterial pressure. Mean arterial pressure was obtained by electronic filtering of the arterial pressure pulse and recorded on a Grass polygraph (model 7D, Grass Instrument Co., Quincy, Mass.). The level of arterial pressure before laparotomy was recorded for comparison among treated and untreated rats of the two strains. The remaining kidney was exposed through an abdominal incision and denervated by stripping the adventitia from both the renal artery and vein and by applying 95% ethanol containing 10% phenol to each vessel to destroy any remaining nerve fibers. The ureter was cannulated near the renal pelvis with slightly tapered PE-50 tubing. The remaining adrenal gland was isolated and removed. Adjustable Silastic balloon cuffs were placed around the aorta both distal and proximal to the renal artery and were inflated at appropriate times during the experiment to adjust renal artery pressure above and below normal resting values. Snare clamps were placed around the superior mesenteric and celiac arteries to elevate renal artery pressure further when necessary. Femoral artery pressure was used to estimate renal artery pressure when the proximal aortic cuff was inflated, and carotid artery pressure was used when the distal aortic cuff was inflated.

A hormone cocktail was infused via the jugular cannula at a rate of 330 μl·kg⁻¹·min⁻¹ (pump model 903, Harvard Apparatus, South Natick, Mass.). The cocktail was composed of aldosterone (66 ng·kg⁻¹·min⁻¹, Sigma), hydrocortisone (33 μg·kg⁻¹·min⁻¹, Sigma), norepinephrine (333 ng·kg⁻¹·min⁻¹, Sigma), and arginine vasopressin (0.17 ng·kg⁻¹·min⁻¹, Sigma) dis-
solved in saline containing 1% albumin (Fraction V Bovine, Sigma). Also included in the cocktail were 2% inulin and 0.1% PAH for the measurement of glomerular filtration rate (GFR) and effective renal blood flow (RBF), respectively. At these concentrations and this infusion rate, plasma levels of these hormones were reported to be elevated eightfold to 10-fold in comparison with normal values obtained in conscious rats.15 This model was designed to minimize neural or hormonal reflex adjustments to the kidney, which may result from using clamps to increase or decrease renal artery pressure.15 On average, surgery was completed within 90 minutes, at which time the abdomen was bathed in 0.9% NaCl and the muscle layer closed to reduce water loss by evaporation. Abdominal temperature was monitored using a thermistor (model 402, Yellow Springs Instruments, Yellow Springs, Ohio) and maintained at 37±0.5°C using a controller (model 73A, Yellow Springs Instruments) and a heat lamp.

**Experimental Protocol**

Two hours after the infusion was started, the pressure-natriuresis curve was characterized as outlined previously4,5 and described below. In control (untreated) SHR and WKY rats, renal artery pressure was lowered to approximately 90 mm Hg by inflating the occluder cuff proximal to the renal artery. After a 20-minute stabilization period, the first 20-minute clearance period was taken. The cuff was then partially released to allow renal artery pressure to increase to approximately 120 mm Hg in both SHR and WKY rats. After a second 20-minute stabilization period, the second 20-minute clearance period was taken. A third 20-minute clearance period was taken 20 minutes after renal artery pressure had been increased to approximately 145 mm Hg by releasing the cuff proximal to the kidney in SHR and in WKY rats by occluding the aorta distal to the renal artery and by clamping the superior mesenteric and celiac arteries. In the SHR, a fourth clearance period had been increased to approximately 175 mm Hg by occluding various vessels as described above for WKY rats.

In enalapril-treated SHR and WKY rats, the same time scale for clearance periods was followed. Ideally, similar renal artery pressures should have been used. However, preliminary studies (not reported) revealed that the range of renal artery pressures attainable in enalapril-treated animals was different from that which could be attained in the respective controls. For clearance 1, renal artery pressure was decreased to approximately 85 mm Hg in both SHR and WKY rats. Renal artery pressure was then increased to approximately 110 mm Hg in both SHR and WKY rats for clearance 2 and further increased in clearance 3 to approximately 135 mm Hg. In a subsequent group of enalapril-treated SHR (SHR2), renal artery pressure was adjusted to obtain values similar to those used in control WKY rats.

**Analytical Techniques**

Urine volume was calculated gravimetrically after collecting urine under oil in preweighed vials. Hematocrit (Hct) was calculated by the microcapillary tube method from arterial blood samples (300 µl) taken at the midpoint of each clearance. The concentrations of PAH and inulin in both plasma and urine were measured by the method of Smith18 and the anthrone method,19 respectively. RBF was calculated as the clearance of PAH divided by (1−Hct), and GFR was calculated as the clearance of inulin. Urine and plasma were analyzed for sodium concentration with a flame photometer (FLM 3, Radiometer, Copenhagen) to determine both the total excretion of sodium (product of urine flow and urinary sodium concentration) and the fractional excretion of sodium (sodium excretion divided by the filtered load of sodium). At the end of each experiment, the rat was killed by injecting a euthanasia solution (saturated KCl and MgSO4), and the kidney was removed, decapsulated, cut in half, blotted dry, and weighed. All renal function measurements are expressed per gram kidney weight.

**Statistical Analyses**

All data are reported as mean±SEM. Renal function measurements obtained at different renal artery pressures within a group were subjected to Bartlett's test for homogeneity of variance. If the variances were homogeneous, then a one-way analysis of variance (ANOVA) with repeated measures was done, and when appropriate, individual means were subjected to the Newman-Keuls test for statistical differences.19 If the Bartlett's test indicated heterogeneity of variance, then the values were converted to natural logarithms, tested using Bartlett's test to ensure homogeneity of variance, and then subjected to a one-way ANOVA. Statistical significance of differences in measured values between groups at similar renal artery pressures was determined using an independent t test. Variables measured during the treatment period were analyzed using a two-way ANOVA and a Duncan's multiple range test.19 Calculated F, t, and χ² values were considered significant if p<0.05.

**Results**

**Arterial Pressure**

Over the duration of the treatment period, both SHR and WKY rats treated with enalapril drank significantly more than the untreated controls (Figure 1). The actual amount of enalapril received per day in the drinking water averaged 26±1 and 24±1 mg·kg⁻¹·day⁻¹ for WKY rats and SHR, respectively, over the 4-week treatment period. Enalapril-treated SHR and WKY rats had a significantly greater body weight when compared with control rats during the first week of treatment, but after the first week there were no significant differences between treated and control animals. Tail-cuff pressure of control SHR was not significantly different compared with that of
control WKY rats until the sixth week of age, after which it continued to increase in SHR but remained stable in WKY rats (Figure 2A). Enalapril-treated SHR and WKY rats had significantly lower tail-cuff pressures when compared with untreated SHR and WKY rats at all ages tested. At 8 weeks of age, there was no statistical difference in tail-cuff pressure between control WKY rats and treated SHR.

Body weight on the day of the experiment varied between 185 and 220 g with no statistical difference between treated animals and their respective controls. The age of the rats ranged between 53 and 67 days for both SHR and WKY rats. Mean arterial pressure under Inactin anesthesia is shown in Figure 2B. Enalapril-treated SHR and WKY rats had significantly lower arterial pressures when compared with their respective controls (control SHR 175±3 mm Hg versus enalapril-treated SHR 124±2 mm Hg, p<0.05; control WKY rats 118±5 mm Hg versus enalapril-treated WKY rats 94±4 mm Hg, p<0.05). There was no significant difference between control WKY rats and enalapril-treated SHR.

Renal Hemodynamics

The effects of changes in renal artery pressure on GFR and RBF are summarized in Table 1. In control WKY rats, GFR at the lowest renal artery pressure was significantly less than the values for GFR at the two higher pressures. Similarly, GFR in control SHR was significantly lower during the first clearance period when compared with the values measured during clearances 2, 3, and 4, which were not significantly different from one another. RBF was autoregulated over the entire pressure range in control WKY rats. In control SHR, the value for RBF in clearance 1 was significantly less than the values obtained during clearances 2, 3, and 4. In enalapril-treated animals, GFR and RBF were both autoregulated over the entire range of pressures used, and there were no significant differences in GFR and RBF between strains. At renal artery pressures where differences in sodium excretion were seen (described below), no significant differences in GFR and RBF existed between any of the five groups of animals.

Pressure-Natriuresis in Control Spontaneously Hypertensive Rats and Wistar-Kyoto Rats

The relation between renal artery pressure and urinary excretion of sodium is shown in Figure 3A. In both control SHR and WKY rats there was a significant effect due to pressure. There was no significant difference in sodium excretion during clearance periods 1 and 2 between SHR and WKY rats. However, in clearance 3 at a renal artery pressure of 145±3 mm Hg in WKY rats and 146±2 mm Hg in SHR, WKY rats excreted a significantly greater amount of sodium when compared with SHR (11.34±1.86 versus 5.64±0.95 μmole/min−1·g kidney wt−1, respectively; p<0.05). The relation between renal artery pressure and urine flow (Figure 3B) or fractional excretion of sodium (FENa+, Figure 3C) mirrored that described above for sodium excretion.

Pressure-Natriuresis in Enalapril-Treated Spontaneously Hypertensive Rats and Wistar-Kyoto Rats

Both groups of enalapril-treated rats showed significant effects of pressure on sodium excretion (Figure 3A), urine flow (Figure 3B), and FENa+ (Figure 3C). When enalapril-treated WKY rats were compared with enalapril-treated SHR, sodium excretion was similar during clearances 1 and 2 (Figure 3A); however, when renal artery pressure was elevated to 136±2 and 132±3 mm Hg during clearance 3 in WKY rats and SHR, respectively, WKY rats excreted twice as much sodium when compared with SHR (13.6±1.94 versus 6.54±1.18 μmole/min−1·g kidney wt−1; p<0.05). Again, differences in urine flow (Figure 3B) and FENa+ (Figure 3C) between treated
WKY rats and SHR mirrored results for sodium excretion.

Enalapril treatment resulted in a shift to the left of the pressure–natriuresis curve of WKY rats so that control and enalapril-treated WKY rats excreted similar amounts of sodium (11.34±1.86 versus 13.60±1.94 μmol-min⁻¹·g kidney wt⁻¹) but at significantly different pressures (145±3 versus 136±2 mm Hg, respectively; \( p < 0.05 \); Figure 3A). The same relation was seen for urine flow (Figure 3B) and FE \(_{\text{Na}^+}\) (Figure 3C). Similarly, the pressure–natriuresis curve for enalapril-treated SHR was shifted to the left compared with control SHR, since control and enalapril-treated SHR excreted a similar amount of sodium (5.64±0.95 versus 6.54±1.18 μmol-min⁻¹·g kidney wt⁻¹) during clearance 3 but did so at significantly different pressures (146±2 versus 132±3 mm Hg; \( p < 0.05 \); Figure 3A). Again the same relation was seen for urine flow (Figure 3B) and FE \(_{\text{Na}^+}\) (Figure 3C). When renal artery pressure was controlled in enalapril-treated SHR (SHR2) at levels similar to those used in control WKY rats, there were no significant differences in renal output of sodium and urine and no difference in the FE \(_{\text{Na}^+}\) (Figures 4A, 4B, and 4C) between the two groups. That is, enalapril treatment of SHR appeared to "normalize" arterial pressure and renal function when compared with untreated WKY rats. Treated SHR (SHR2, Figure 4A) had a sodium excretion of 9.16±1.27 μmol-min⁻¹·g kidney wt⁻¹ at 143±1 mm Hg, whereas sodium excretion in control SHR (Figure 3A) at 146±2 mm Hg was 5.64±0.95 μmol-min⁻¹·g kidney wt⁻¹ (\( p < 0.05 \)).

Discussion

Previous studies have shown that the pressure–natriuresis curve is shifted to the right in 6–9-week-old SHR when compared with that in age-matched WKY rats.\(^5\) The explanation for this shift is not clear, but it was attributed to differences in both GFR and tubular reabsorption in SHR. In the present study, we confirmed the observation of a difference between the pressure–natriuresis curves of 7–9-week-old SHR and WKY rats, although in our hands altered tubular reabsorption of sodium appeared to be more dominant since there were no significant differences in GFR or RBF between the two strains at renal

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**Figure 2.** Bar graphs showing effect of chronic enalapril treatment on spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. Panel A: Average weekly tail-cuff pressure of control and enalapril-treated (25 mg·kg⁻¹·day⁻¹) rats. Panel B: Mean arterial pressure of control and enalapril-treated rats, 7–9 weeks of age, under Inactin anesthesia. Letters above bars indicate statistical differences among groups for a given age: bars with different letters differ significantly (\( p < 0.05 \)) from one another as determined by two-way analysis of variance and Duncan's multiple range test. Each bar represents mean±SEM of 10–24 rats.
The similarity between the pressure–natriuresis curves of SHR and WKY rats at the low renal artery pressures used in this preparation may be due to the sodium-retaining components of the hormone cocktail overriding the pressure–natriuresis mechanism at low renal artery pressures. On the other hand, an altered sensitivity to one or more of the infused hormones could also contribute in part to the difference in the pressure–natriuresis curves at higher renal artery pressures in SHR and WKY rats. For example, Krayacich et al. have shown that the dose of norepinephrine used in this study has direct effects on renal function and that kidneys with different sensitivities to norepinephrine had significantly altered pressure–natriuresis responses. Moreover, Rudd et al. have suggested that WKY rats may be less sensitive to the tubular actions of norepinephrine compared with SHR and other strains since acute renal denervation failed to produce the characteristic denervation natriuresis in the WKY rat. Takezawa et al. have shown that an infusion of a synthetic atrial peptide shifts the pressure–natriuresis relation of normotensive rats to the left; therefore, it is possible that changes in endogenous atrial natriuretic peptide (ANP) in response to the volume load may have affected the position of the pressure–natriuresis curve. Although an acute volume load has been shown to produce similar increases in plasma ANP levels in both SHR and WKY rats, the natriuretic response to a given amount of ANP is dependent on the level of renal artery pressure. For example, at a pressure of 145 mm Hg a greater effect of ANP would be expected in the WKY rats when compared with SHR at the same pressure because that pressure would be “high” for the WKY rat but “low” for the SHR. However, this does not explain the intrinsic difference between the pressure–natriuresis curves of the two strains.

The effect of renal artery pressure and ANP on sodium excretion is also influenced by the presence or absence of Ang II, another circulating and intrarenal factor not controlled in this preparation and known to modulate the pressure–natriuresis response. In theory, an enhanced influence of Ang II on the SHR kidney could explain the blunted

### Table 1. Effect of Acute Elevations in Renal Artery Pressure on Renal Hemodynamics in Control and Enalapril-Treated Wistar-Kyoto and Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>RAP (mm Hg)</th>
<th>GFR (ml/min/kg kidney wt⁻¹)</th>
<th>RBF (ml/min/kg kidney wt⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control WKY</td>
<td>89±2</td>
<td>0.79±0.07*</td>
<td>4.02±0.23</td>
</tr>
<tr>
<td></td>
<td>117±3</td>
<td>1.13±0.10</td>
<td>4.80±0.54</td>
</tr>
<tr>
<td></td>
<td>145±3</td>
<td>1.12±0.11</td>
<td>4.42±0.41</td>
</tr>
<tr>
<td>Enalapril WKY</td>
<td>86±2</td>
<td>0.82±0.06</td>
<td>4.51±0.34</td>
</tr>
<tr>
<td></td>
<td>112±2</td>
<td>0.81±0.07</td>
<td>4.66±0.35</td>
</tr>
<tr>
<td></td>
<td>136±2</td>
<td>1.04±0.20</td>
<td>4.58±0.41</td>
</tr>
<tr>
<td>Control SHR</td>
<td>90±2</td>
<td>0.55±0.10**†</td>
<td>3.55±0.38**†</td>
</tr>
<tr>
<td></td>
<td>118±3</td>
<td>0.99±0.15</td>
<td>4.87±0.52</td>
</tr>
<tr>
<td></td>
<td>146±2</td>
<td>0.98±0.08</td>
<td>4.49±0.35</td>
</tr>
<tr>
<td></td>
<td>176±3</td>
<td>0.94±0.10</td>
<td>4.20±0.55</td>
</tr>
<tr>
<td>Enalapril SHR</td>
<td>84±2</td>
<td>0.79±0.08</td>
<td>4.01±0.38</td>
</tr>
<tr>
<td></td>
<td>107±2</td>
<td>0.83±0.09</td>
<td>4.12±0.31</td>
</tr>
<tr>
<td></td>
<td>132±3</td>
<td>0.90±0.07</td>
<td>4.22±0.34</td>
</tr>
<tr>
<td>Enalapril SHR2</td>
<td>91±1</td>
<td>0.80±0.10</td>
<td>4.31±0.41</td>
</tr>
<tr>
<td></td>
<td>124±2</td>
<td>0.99±0.08</td>
<td>4.95±0.30</td>
</tr>
<tr>
<td></td>
<td>143±1</td>
<td>1.00±0.11</td>
<td>4.12±0.60</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. RAP, renal artery pressure; GFR, glomerular filtration rate; RBF, renal blood flow; SHR2, a second group of enalapril-treated spontaneously hypertensive rats.

*Indicates a significant difference (p<0.05) when compared with other values within a group.

†Indicates a significant difference (p<0.05) between control SHR and enalapril-treated SHR during a similar clearance period.

The significant effect of pressure on FE N⁺⁺ in both SHR and WKY rats is consistent with a major involvement of changes in tubular reabsorption of sodium in the pressure–natriuresis response in general. Current evidence suggests that changes in intrarenal hemodynamics may play an important role in the pressure–natriuresis mechanism, and it is possible that although GFR was not significantly different between groups, intrarenal hemodynamics may have been altered. Of interest are the recent studies suggesting that the pressure–natriuresis curve in SHR may be displaced along the pressure axis when compared with that in WKY rats due to altered medullary hemodynamics and blunted responses of renal interstitial hydrostatic pressure to changes in renal artery pressure. Moreover, structural differences in the renal vasculature between SHR and WKY rats may contribute to the latter two observations that have been described.

The similarity between the pressure–natriuresis curves of SHR and WKY rats at the low renal artery pressures used in this preparation may be due to the sodium-retaining components of the hormone cocktail overriding the pressure–natriuresis mechanism at low renal artery pressures. On the other hand, an altered sensitivity to one or more of the infused hormones could also contribute in part to the difference in the pressure–natriuresis curves at higher renal artery pressures in SHR and WKY rats. For example, Krayacich et al. have shown that the dose of norepinephrine used in this study has direct effects on renal function and that kidneys with different sensitivities to norepinephrine had significantly altered pressure–natriuresis responses. Moreover, Rudd et al. have suggested that WKY rats may be less sensitive to the tubular actions of norepinephrine compared with SHR and other strains since acute renal denervation failed to produce the characteristic denervation natriuresis in the WKY rat. Takezawa et al. have shown that an infusion of a synthetic atrial peptide shifts the pressure–natriuresis relation of normotensive rats to the left; therefore, it is possible that changes in endogenous atrial natriuretic peptide (ANP) in response to the volume load may have affected the position of the pressure–natriuresis curve. Although an acute volume load has been shown to produce similar increases in plasma ANP levels in both SHR and WKY rats, the natriuretic response to a given amount of ANP is dependent on the level of renal artery pressure. For example, at a pressure of 145 mm Hg a greater effect of ANP would be expected in the WKY rats when compared with SHR at the same pressure because that pressure would be "high" for the WKY rat but "low" for the SHR. However, this does not explain the intrinsic difference between the pressure–natriuresis curves of the two strains.

The effect of renal artery pressure and ANP on sodium excretion is also influenced by the presence or absence of Ang II, another circulating and intrarenal factor not controlled in this preparation and known to modulate the pressure–natriuresis response. In theory, an enhanced influence of Ang II on the SHR kidney could explain the blunted
pressure–natriuresis response in SHR. To test whether the renin-angiotensin system may contribute to the altered pressure–natriuresis curve in SHR, we treated SHR and WKY rats with enalapril for 4 weeks before determining pressure–natriuresis responses in anesthetized rats. We reasoned that if an
enhanced effect of Ang II, either circulating or intrarenal, were responsible for the shift in the pressure–natriuresis curve and thereby contributed to the hypertensive process in SHR, then chronic administration of enalapril, which is known to prevent hypertension in SHR,6–8 should normalize the pressure–natriuresis curve.

In our study, chronic administration of enalapril in tap water had a significant effect on arterial pressure in SHR and WKY rats throughout the duration of treatment. Rats of both strains had significantly elevated water intake while they were treated with enalapril, and this also persisted throughout the treatment period. This effect of chronic converting enzyme inhibition on water intake has been reported by others,7 although the mechanism of this effect is not entirely clear. At 8 weeks of age, arterial pressure in treated SHR was not significantly different from that in control WKY rats, but enalapril also decreased arterial pressure significantly in WKY rats. Interestingly, the pressure–natriuresis curves of treated SHR and WKY rats were both shifted to the left when compared with their respective untreated controls, with the pressure–natriuresis curve for the treated SHR being superimposed on that for the untreated WKY rats. In other words, the relative positions of the acute pressure–natriuresis curves were in agreement with the relative levels of arterial pressure (tail-cuff or mean arterial pressure under anesthesia) in the various groups of rats. These observations are consistent with the proposal that the ability of the kidney to alter sodium and water output when exposed to acute alterations in renal artery pressure is a major determinant of the chronic level of arterial pressure.34

The explanation for the shift of the pressure–natriuresis curve in both SHR and WKY rats treated with enalapril is not clear, although the enhanced pressure–natriuretic response in this volume-expanded preparation is consistent with what would be expected if Ang II normally modulates the response similarly in both strains. The fact that the pressure–natriuresis curve for the treated SHR was still shifted along the pressure axis when compared with the curve in treated WKY rats suggests that factors other than the renin-angiotensin system are responsible for the difference between SHR and WKY rats seen in this preparation. These could include components in the hormone cocktail, structural differences, or other uncontrolled circulating or intrarenal modulators of pressure–natriuresis. The findings that SHR have altered medullary hemodynamics23 and blunted responses of renal interstitial hydrostatic pressure24,25 to changes in renal artery pressure support an intrarenal cause for the difference between SHR and WKY rats, rather than a change induced by the preparation itself.

In contrast to the findings reported here, the preliminary report of Takenaka et al35 suggested that the renin-angiotensin system does contribute to the difference between pressure–natriuresis curves in SHR and WKY rats. They used a similar preparation but administered enalapril acutely, directly into the kidney. Although it is not clear what age of rat was used, according to their results, enalapril shifted the pressure–natriuresis curve of the SHR to the left, but did not alter the curve in WKY rats. Why enalapril had no effect on the pressure–natriuresis curve of WKY rats is not clear, as other studies have shown Ang II to be a modulator of pressure–natriuresis in normotensive animals.33 The fact that Takenaka et al35 used acute and we used chronic administration of enalapril could also account for differences in the results, since chronic enalapril treatment of young rats is reported to also alter structural properties of the circulation.36

In conclusion, the acute pressure–natriuresis curves of volume-loaded SHR with fixed neural and hormonal influences on the kidney were shifted significantly to higher renal artery pressures when compared with WKY rats under similar conditions. This difference was due to tubular mechanisms as GFR and RBF were not significantly different between strains. SHR and WKY rats chronically treated with enalapril had significantly lower arterial pressure than their untreated controls. Pressure–natriuresis curves in enalapril-treated SHR were similar to those in untreated WKY rats when tested over a similar range of renal artery pressures, but enalapril treatment also shifted the pressure–natriuresis curve of WKY rats to lower renal artery pressures. The persistent difference between pressure–natriuresis curves in treated SHR and treated WKY rats was attributed to differences in FEN+, thereby implicating tubular mechanisms. The similar shift of the pressure–natriuresis curve in enalapril-treated SHR and WKY rats suggests that the renin-angiotensin system is not a major factor responsible for the differences noted between pressure–natriuresis curves of untreated SHR and WKY rats in this preparation.

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